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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/724,108	12/01/2003	Hideki Thoda	245694US0CONT	3217

22850 7590 05/22/2006

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EXAMINER	
SCHLAPKOHL, WALTER	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 05/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/724,108	THODA ET AL.	
	Examiner	Art Unit	
	Walter Schlapkohl	1636	uaj

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of the papers filed on 3/2/2006. Claims 1-13 are pending.

Election/Restrictions

Applicant's arguments with regard to the restriction (election) requirement have been carefully considered and found persuasive. Applicant's arguments in the traversal of the restriction requirement are thereby rendered moot.

Information Disclosure Statement

The information disclosure statement filed 2/2/2004 fails to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information

disclosure statement. The information disclosure statement has been placed in the application file, but the information referred to therein has not been considered.

Oath/Declaration

Applicant is now required to submit a substitute declaration or oath to correct the following deficiencies: the spelling of Inventor Hideki Tohda does not match the printed version of his name on either the Oath/Declation or the ADS. It is also noted that Inventor Tohda is a patent holder and has used the name "Tohda" on all previous patents. The substitute oath or declaration must be filed within the THREE MONTH shortened statutory period set for reply in the "Notice of Allowability" (PTO-37). Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136. Failure to timely file the substitute declaration (or oath) will result in **ABANDONMENT** of the application. The transmittal letter accompanying the declaration (or oath) should indicate the date of the "Notice of Allowance" (PTOL-85) and the application number in the upper right hand corner.

Specification

The disclosure is objected to because of the following informalities: the continuity data of the instant application is not recited in the first line of the specification.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2, 4-5, 7-8, 10-11 & 13, and therefore dependent claims 3, 6, 9 and 12, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the term "transgenically introduced" in line 3. Claim 1 is vague and indefinite in that the meaning of "transgenically introduced" is unclear. Does Applicant intend any gene which is recombinantly introduced, any gene which is introduced as a transgene (in contrast to a gene knock-out) or any heterologous gene inserted "in trans" to the native host gene.

Claim 1 also recites "part or all of the genome of a eukaryotic host microorganism unnecessary or detrimental to production of the heterologous protein by a transformant of the host in culture for the purpose of improving productivity of the heterologous protein" in lines 4-8. Claim 1 is also vague and indefinite in that the metes and bounds of "unnecessary and detrimental" are unclear. Does the claim encompass portions of the host microorganism's genome which are "unnecessary" for short term production of the heterologous protein but which may alter the viability or growth characteristics of the eukaryotic host microorganism, or does Applicant intend to encompass only those genes which are "unnecessary or detrimental" to the viability and growth of the host as well as "unnecessary or detrimental" to the host's ability to produce the heterologous protein? Claim 1 is also vague and indefinite in that the phrase "improving productivity of the heterologous protein" is unclear. Does Applicant intend such a method wherein the production of the heterologous protein is increased by deletion or inactivation of part or all of the genome of the host or does Applicant intend such a method wherein the activity or some other production-related characteristic of the heterologous protein is improved?

Claim 2 recites "[t]he method according to Claim 1, wherein the part of the genome unnecessary or detrimental to production of the heterologous protein by the transformant in culture is genes associated with energy metabolism, proteases, meiosis, transcription, cell growth and division and DNA synthesis, transcription, protein synthesis, membrane transport, cell structure maintenance, signal transduction or ion homeostasis in the eukaryotic host microorganism" in lines 1-8. Claim 2 is vague and indefinite in that the metes and bounds of "associated with" are unclear? Does Applicant intend to encompass genes which are, e.g., directly involved in signal transduction or a more broader category of such genes, such as genes which regulate the transcription of genes that are directly involved in signal transduction?

Similarly, claim 4 recites "[t]he method according to Claim 3, wherein the part of the genome of *Schizosaccharomyces pombe* unnecessary or detrimental to production of the heterologous protein by the transformant in culture is a gene selected from the genes associated with energy metabolism and the genes associated with proteases" in lines 1-6. Claim 4 is vague and indefinite in that the metes and bounds of the phrases "unnecessary or detrimental" and "associated with" are unclear as explained above.

Claim 5 recites the phrase "transgenically introduced gene" in lines 2-3. Claim 5 is vague and indefinite in that the meaning of "transgenically introduced is unclear as explained above.

Claim 7 recites "[a] transformant obtained by introducing the structural gene encoding a heterologous protein into a eukaryotic host microorganism in which part or all of the genome of the eukaryotic host microorganism unnecessary or detrimental to production of the heterologous protein by the transformation in culture has been deleted or inactivated..." in lines 1-7. Claim 7 is vague and indefinite in that "the structural gene" lacks proper antecedent basis; there is no reference to a structural gene in the claim prior to the recitation of "the structural gene in lines 1-2. Claim 7 is also vague and indefinite in that the metes and bounds of "unnecessary or detrimental" are unclear as explained above.

Similarly, claim 8 is vague and indefinite in that the metes and bounds of the phrases "unnecessary or detrimental" and "genes associated with" various cell functions are unclear as explained above.

Claims 10 recites "[a] method of producing a heterologous protein, comprising causing a transformant of a eukaryotic host microorganism having a gene encoding a heterologous protein

extrinsic to the host" in lines 1-4. Claim 10 is vague and indefinite in that it is unclear whether Applicant intends a method of producing a heterologous protein comprising constructing a eukaryotic host, wherein the the host is transformed with a gene encoding a heterologous protein that is inessential to the host or whether Applicant intends a method of producing a heterologous protein by creating a transformed host organism capable of producing the heterologous protein while the gene remains outside of the host.

Claim 10 further recites such a method "wherein the productivity of the heterologous protein is improved by deleting or inactivating part or all of the genome of the eukaryotic host microorganism which is unnecessary or detrimental to production of the heterologous protein by the transformant in culture" in lines 5-10. Claim 10 is vague and indefinite in that it is unclear whether Applicant intends such a method wherein the production of the heterologous protein is increased by deletion or inactivation of part or all of the genome of the host or whether Applicant intends such a method wherein the activity or some other production-related characteristic of the heterologous protein is improved. Claim 10 is also vague and indefinite in that the metes and bounds of "unnecessary or detrimental" are unclear as explained above.

Claims 11 and 13 recite the phrases "unnecessary or detrimental" and "genes associated with" various cell functions. These claims are vague and indefinite because the metes and bounds of such phrases are unclear as explained above.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of constructing a eukaryotic host microorganism for production of a heterologous protein encoded by a transgene, the method being characterized by deleting or inactivating part or all of the genome of a eukaryotic host microorganism unnecessary or detrimental to production of the heterologous protein for the purpose of

improving the productivity of the heterolgous protein. Some claims are further limited to such a method wherein the part of the genome unnecessary or detrimental to production of the heterologous protein by the transformant is genes associated with energy metabolism, proteases, meiosis, transcription , cell growth and division and DNA synthesis, protein synthesis, membrane transport, cell structure maintenance, signal transduction or ion homeostasis. Some claims are further limited to such a method wherein the eukaryotic microorganism is *Schizosaccharomyces pombe*. The claims encompass the production of any heterologous protein by any eukaryotic microorganism host wherein any part or all of the genome "unnecessary or detrimental" to production of the heterologous protein is either deleted or otherwise inactivated. The claims are also drawn to such a eukaryotic host made by such methods. The claims do not provide any structural information with regard to the heterologous proteins which can be produced in combination with unnecessary or detrimental parts of the genome, however comprehensive or focused, such that the host is capable of "improving the productivity of the heterologous protein." The claims also do not provide any structural information about which eukaryotic microorganism hosts would be capable of producing which heterologous proteins in combination with which

deletions of the host's genome such that a heterologous protein's production is improved. Thus, the rejected claims comprise a set methods and eukaryotic microorganism hosts that are defined by the function of the host in and the function of the deleted or inactivated portions of the host's genome.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. The specification lists some genes which are unnecessary or detrimental to production of a heterolgous protein in S. pombe such as pyruvate decarboxylase, aminopeptidase and carboxypeptidease (see, e.g. page 5, lines 20-27). The specification further lists yeast of the Saccharomyces genus and Pichia genus as preferable (see, e.g., page 6, lines 1-7). The specification also teaches that the part of the genome unnecessary or detrimental to production of the heterologous protein by the tranformant "may be genes essential for the wild type host to survive or grow, because such essential genes are not always necessary to a transformant culture" (page 7, lines 6-10). The specification also lists

preferred examples of a number of genes considered by Applicant to be unnecessary or detrimental to production of the heterologous protein such as genes involved in energy metabolism (e.g., pyruvate decarboxylase which is involved in ethanol fermentation), genes associated with proteases such as endopeptidases and serine proteases. As examples of the instantly claimed invention, the specification describes *S. pombe* transformants which produce green fluorescent protein (GFP) efficiently by inactivation of a pyruvate decarboxylase gene, a serine protease gene, an aminopeptidase gene, a carboxypeptidase gene, an aspartic protease gene, a dipeptidyl aminopeptidase gene, a vacuolar carboxylase gene, a zinc protease gene, a metalloprotease gene, a CAAX prenyl protease gene, a dipeptidase gene, a methionine metallopeptidase gene, a methionine aminopeptidase gene, a signal peptidase gene and a mitochondrial processing peptidase gene. No description is provided of such a method or host, wherein the host eukaryotic microorganism is anything by a yeast of the species *S. pombe*. No description is provided of such a method or host, wherein the heterolgous protein produced is any other than GFP. No description is provided of such a method or host wherein the deleted or inactivated portion of the genome is a gene involved

in, e.g., meiosis or transcription or wherein the portion of the genome deleted is a non-coding region of the genome.

Even if one accepts that the examples described in the specification meet the claim limitations of the rejected claims with regard to structure and function, the examples are only representative of one species of eukaryotic host microorganism and one type of heterologous protein in the context of, at most, 13 classes of disrupted genes. The results are not necessarily predictive of any other eukaryotic microorganism host, any other heterologous protein or any other class of disrupted gene. Thus it is impossible to extrapolate from the examples described herein those hosts in combination with those heterologous proteins in combination with those deleted or inactivated portions of the host's genome that would necessarily meet the structural/functional characteristics of the rejected claims.

The prior art does not appear to offset the deficiencies of the instant specification in that it does not describe a set of eukaryotic microorganism hosts comprising deleted or inactivated genes or genomic regions such that there is improved production of a heterologous protein. A review by Giga-Hama and Kumagai describes the production of many heterologous proteins in *S. pombe*, but does not provide a single example of such a eukaryotic host in which a portion of the eukaryotic host's

genome was deleted or inactivated in order to increase "the productivity of the heterologous protein" (*Biotechnology and Applied Biochemistry* **30**:235-244, 1999). Egel-Matani et al (U.S. Patent No. 6,110,703) teach the inactivation of the yeast Yap3 gene in order to improve production of a heterologous polypeptide within a transformed *S. pombe* host, but they do not teach such a method wherein any portion of the host genome unnecessary or detrimental to the production of the heterologous protein can be deleted or inactivatd such that the production of the heterologous protein is improved.

Given the very large genus of eukaryotic microorganism hosts, the very large genus of heterologous proteins, and the very large genus of genomic deletions encompassed by the claims, and given the limited description provided by the prior art and specification with regard to the combinations of eukaryotic microorganism hosts, regions of genomic disruption/inactivation and heterologous proteins capable of fulfilling the claim limitations of claims 1-13, the skilled artisan would not have been able to describe the broadly claimed genus of methods and hosts comprising eukaryotic microorganisms with genomic deletions/inactivation such that a heterologous protein is produced and the "productivity of the heterologous protein" is improved. Thus, there is no structural/functional basis

provided by the prior art or instant specification for one of skill in the art to envision those hosts/heterologous proteins/deleted or inactive regions of the genome that satisfy the functional limitations of the claims. Therefore, the skilled artisan would have reasonably concluded Applicant was not in possession of the claimed invention for claims 1-13.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Egel-Mitani et al (US Patent No. 6,110,703).

Note: for purposes of this rejection only, Examiner has interpreted the claims to be drawn to a method of constructing a eukaryotic host microorganism for production of a heterologous protein encoded by a transgene, wherein part or all of the genome of the eukaryotic host microorganism unnecessary to production of the heterologous protein has been deleted or

inactivated in order to improve the production of the heterologous protein by the host.

Egel-Mitani et al teach a method of constructing a transformed eukaryotic host microorganism for the production of a heterologous polypeptide wherein the host has inactive Yap3 protease which prevents the degradation of the heterologously produced protein (see entire document, especially column 19, claim 1 and column 20, claim 11, as well as columns 10-12, Examples 6-10). Egel-Matani et al teach such a method wherein the eukaryotic host microorganism is *S. pombe* (see, e.g. column 4, lines 7-12; and column 20, claim 11). Regarding claim 10, Egel-Matini et al teach the collection of the heterologous protein by HPLC elution or general purification steps (see, e.g., column 11, lines 3-4; and column 19, claim 1). Because Yap3 is a protease, the method and hosts of Egel-Matani et al meets the claim limitation of claims 2, 4, 8, 11 and 13.

Claims 1-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Simeon et al (*Yeast* **11**:271-282, 1995; IDS Ref. AW).

Note: for purposes of this rejection only, Examiner has interpreted the claims to be drawn to a method of constructing a eukaryotic host microorganism for production of a heterologous

protein encoded by a transgene, wherein part or all of the genome of the eukaryotic host microorganism unnecessary to production of the heterologous protein has been deleted in order to improve the production of the heterologous protein by the host.

Simeon et al teach a method of constructing a *Schizosaccharomyces pombe* eukaryotic host microorganism for the production of a heterologous protein, Carboxypeptidase Y of *Saccharomyces cerevisiae* (CY^{sc}) (see entire document, especially pages 271-272). Simeon et al teach such a method wherein the endogenous *S. pombe* Carboxypeptidase Y gene has been inactivated by exposure to ethylmethanesulfonate (EMS) and subsequence screening for *S. pombe* clones devoid of endogenous Carboxypeptidase Y (CY^{sp}) activity (see page 272, second column, first paragraph). Regarding claim 10, Simeon et al teach the collection of the heterologous protein by sucrose density centrifugation (see page 277, Figure 3). Because CY^{sc} is a protease, the method of Simeon et al meets the claim limitation of claims 2, 4, 8, 11 and 13. Importantly, although Simeon et al do not teach such a method wherein the endogenous carboxypeptidase disruption results in improved production of the heterologous protein, such is the case inherently based upon Applicant's admission in the specification that "deletion or

inactivation of part or all of the genome of the host unnecessary or detrimental to production of the heterologous protein by its transformant improves the production efficiency of the heterologous protein" (see instant specification at page 3, lines 24-27 and page 4, line 1).

Claims 1-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Sharma et al (*Curr. Genet.* **38**:71-77, 2000; IDS Ref. AX).

Note: for purposes of this rejection only, Examiner has interpreted the claims to be drawn to a method of constructing a eukaryotic host microorganism for production of a heterologous protein encoded by a transgene, wherein part or all of the genome of the eukaryotic host microorganism unnecessary to production of the heterologous protein has been deleted in order to improve the production of the heterologous protein by the host.

Sharma et al teach a method of constructing a *Schizosaccharomyces pombe* eukaryotic host microorganism for the production of a heterologous protein, thioredoxin (TRX1) (see entire document, especially pages 72, second column, 3rd paragraph; and page 76, first column, last paragraph). Sharma et al teach such a method wherein the endogenous *S. pombe* γ-

glutamyl-cystein synthetase (gcs1) gene has been disrupted (see page 72, Table 1 and second column, last paragraph). Because gcs1 is associated with energy metabolism, at a minimum insofar as it's role in the production of compound important to maintenance of the redox environment and protection from oxidative stress are concerned (see, e.g., page 71, 2nd column, first paragraph), the method of Sharma et al meets the claim limitation of claims 2, 4 and 8. Importantly, although Sharma et al do not teach such a method wherein the endogenous gcs1 disruption results in improved production of the heterologous protein, such is the case inherently based upon Applicant's admission in the specification that "deletion or inactivation of part or all of the genome of the host unnecessary or detrimental to production of the heterologous protein by its transformant improves the production efficiency of the heterologous protein" (see instant specification at page 3, lines 24-27 and page 4, line 1).

Conclusion

Certain papers related to this application may be submitted to the Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax

telephone number for the Group is (571) 273-8300. Note: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent applications to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at (800) 786-9199.

Any inquiry concerning rejections or objections in this communication or earlier communications from the examiner should

be directed to Walter Schlapkohl whose telephone number is (571) 272-4439. The examiner can normally be reached on Monday through Thursday from 8:30 AM to 6:00 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached at (571) 272-0781.

Walter A. Schlapkohl, Ph.D.
Patent Examiner
Art Unit 1636

May 11, 2006

NANCY VOGEL
PRIMARY EXAMINER